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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,049	DE KRETSER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-16,18-22,27-30 and 61-71* is/are pending in the application.

4a) Of the above claim(s) *8,9,13-16,20-22 and 27-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-7, 10-12, 18, 19, 30 and 61-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/14/2011 has been entered.

2. Claims 1-2, 5-16, 18-22, 27-30, and 61-71 are pending.

3. Claims 8, 9, 13-16, 20-22 and 27-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 are under examination as they read on a method of modulating the inflammatory response/therapeutically and/or prophylactically treating a condition, wherein modulating is downregulation of activin functional activity, achieved by introducing a proteinaceous molecule which functions as an antagonist of the activin expression product, wherein the antagonist is follistatin, and (i) airway inflammation as the specific condition; (ii) an acute inflammatory response; and (iii) targeting activin A.

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claim 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-5, 22, 23, and 25-35 of copending Application No. 12/399,610. Although the conflicting claims are not identical, they are not patentably distinct from each other because the `610 application is directed to the use of follistatin in the treatment of disease associated with the fibrosis in the liver. The instant application is directed to the use of follistatin for downregulating the inflammatory responses. Inflammation is a disease that is associated with liver fibrosis such as cirrhosis. The specification on page 1, lines 19-20 discloses diseases associated with fibrosis inlcudes cirrhosis of the liver, pulmonary fibroses, and inflammatory bowel disease such as Crohn's disease

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 61, 68-69 and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The "said downregulation of the inflammatory response" recited in claim 68, lacks sufficient antecedent basis in base claim 2. Base claim 2 only recites "inappropriate inflammatory response".

B. The "said pro-inflammatory cytokine cascade" recited in claim 69, lacks sufficient antecedent basis in base claim 2.

C. The recitation "follistatin 288 or follistatin 315" in claims 61 and 71 is ambiguous. It is not clear what is follistatin 288 or 315 stand for.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 are rejected under 35 U.S.C. 102(b) as being anticipated by WO/ 2003/006057 (IDS Reference).

The `057 publication teaches and claims a method of a method for the treatment of disease associated with fibrosis in a vertebrate in need of said treatment, wherein said method comprises

administering to said vertebrate, a therapeutically effective amount of at least one activin antagonist (see published claim 24). The `057 publication further teaches a method for the treatment of disease associated with fibrosis in a vertebrate in need of said treatment, wherein said method comprises administering to said vertebrate, a therapeutically effective amount of the pharmaceutical composition comprising a activin antagonist such as follistatin, or a fragment(s) or analogue thereof (see published claims 2 and 25), wherein the follistatin is a single chain protein comprising between 288 and 315 amino acids (see published claim 3, wherein the vertebrate is selected from the group consisting of human, non-human primate, mice, cattle, sheep, goats, horses, rabbits, birds, cats and dogs (see published claims 27 and 28), wherein the disease associated with fibrosis is one of: inflammatory fibrotic disease; a pulmonary fibrosis (airway inflammation); an inflammatory bowel disease, or a related condition such as ulcerative colitis or Crohn's Disease (see published claim 29). The `057 publication teaches that interstitial lung disease (ILD) referred to as interstitial pulmonary fibrosis or pulmonary fibrosis. The lung is usually damaged in some way, resulting in inflammation in the walls of the air sacs (alveolitis), in the walls of the bronchioles (bronchiolitis) or in the capillaries (vasculitis) (see page 1, lines 20-18).

While the prior art teachings may be silent as to the "the downregulation of the inflammatory response is achieved by modulating the pro-inflammatory cytokine cascade" in claims 18-19 and 68-69 per se; the method, the product used in the reference method are the same as the claimed method. Therefore "modulating the pro-inflammatory cytokine cascade" is considered inherent properties.

Further, since the reference teaches treating the same claimed disease, then the claimed local inflammatory response in claim 62, and the acute inflammatory response in claim 63 is considered inherent to the claimed diseases.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 01/14/2011, have been fully considered, but have not been found convincing.

Applicant argues that fibrosis may occur subsequent to an inflammatory response but fibrosis is not the inflammatory response itself. Fibrosis, instead, is a form of scarring. The fact that inflammatory and fibrosis may occur sequentially is irrelevant to the treatment of inflammation. Moreover, even if fibrosis is successfully treated in a subject, i.e., the scarring is prevented-this result is not necessarily achieved via down-regulation of an inflammatory response.

However, the diseases which are associated with fibrosis such as cirrhosis of the liver, pulmonary fibroses, and inflammatory bowel disease such as Crohn's disease are inflammatory diseases. Further the reference does not teach treating fibrosis as applicant appears to argue, rather the reference teaches the use of follistatin in a method for the treatment of disease associated with fibrosis, inflammation is associated with fibrosis.

While Applicant does not dispute that fibrosis can occur after an inflammatory response, as is the case with interstitial lung disease where an inflammatory response ultimately leads to development of fibrotic tissue. However, follistatin in the context of the `057 publication is taught to be used to modulate fibrotic processes, not inflammatory processes. Although the diseases which are listed at page 3, lines 30-33 of the `057 publication mention inflammatory fibrotic diseases, the fact is that the disclosure is directed to treating the fibrotic processes-scarring-not the inflammatory aspects of these diseases. Applicant submits that there is no teaching in the `057 publication of modulation of the inflammatory response, such as an inflammatory response which does not lead to a fibrotic outcome, rather, the`057 publication is directed to the cellular events of fibrosis, which occur separately form and subsequently to the earlier inflammatory response.

Contrary to applicant assertion, the follistatin in the `057 publication is used to treat diseases associated with fibrosis such as interstitial lung disease, but not fibrosis itself, wherein an inflammatory response ultimately leads to development of fibrotic tissue, as Applicant admits. Further, as is evidenced by instant claim 7, that inflammatory responses occur in the context of airway inflammation such as interstitial lung disease.

Applicant argues that the effects of the inflammatory cytokine cascade are critical to the management of, e.g., septicemia, which kills patients well before a fibrotic response commences. In a reference cited previously by Applicants, mice died within twenty-four hours of an LPS challenge, well before the fibrotic response could occur. As taught by the present application, follistatin can prevent this mortality by downegulating the inflammatory response. In contrast, the '057 publication teaches that in any condition where fibrosis occurs, irrespective of whether it is preceded by an inflammatory response, follistatin can be used to down regulate the fibrotic events. This is markedly different to that which is claimed in the present application wherein one can modulate an inflammatory response irrespective of whether or not fibrosis occurs. The '057 publication teaches that where a fibrotic outcome is associated with an inflammatory condition, the tissue scarring aspect can be down-regulated; however, the preceding inflammatory response will still occur. The fact that the '057 publication teaches that follistatin can down regulate fibroblast stimulation does not teach anything about the regulation of inflammatory responses. Thus, because many inflammatory responses are not associated with fibrosis, and fibrosis occurs at a later time point to inflammation, the '057 publication is distinguished from does not anticipate the claimed invention.

Again, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which follistatin alleviates inflammatory responses does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

11. Claims 1, 2, 5-7, 10-12, 18, 19, 23, 26, 30 and 62-70 are rejected under 35 U.S.C. 102(b) as being anticipated by US 20020192216 as is evidenced by van Eyll et al (Jounal of Cell Science 117(10):2077-2086, 2004).

The `216 publication teaches a method of treating inflammation (see published claims 1 and 11), adult respiratory distress syndrome, chronic obstructive airway disorders such as asthma or emphysema (published claim 29), idiopathic interstitial lung diseases (see published claims 7, 26, 41), multiple sclerosis, rheumatoid arthritis (see published claim 9), comprising administering, to a patient in need thereof, a therapeutically effective amount of an inhibitor of a Hedgehog signalling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signalling pathway (see published claim 1), wherein the inhibitor is Follistatin. The `216 publication teaches a method of treating comprising administering, to a patient in need thereof, a therapeutically effective amount of an inhibitor of a Hedgehog signalling pathway, or an inhibitor of a pathway which is a target of the Hedgehog signalling pathway (see published claim 7). Follistatin has been found to inhibit others aspects of BMP activity as well as acting as an activin-binding protein (¶78 and Table 3). van Eyll et al teach that sonic hedgehog (Shh) signaling can be triggered by activin A and inhibited by follistatin (see page 2085 last ¶).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the follistatin polypeptide in the absence of evidence to the contrary.

The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which follistatin alleviates symptoms of inflammation does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The reference teachings anticipate the claimed invention.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 01/14/2011, have been fully considered, but have not been found convincing.

Applicant submits that the '216 publication discloses that follistatin is an inhibitor of the Hedgehog signaling pathway. As Applicants have argued previously, the Hedgehog signaling pathway does not include activin and it is therefore not entirely clear how this prior art reference

is relevant to the claimed invention. Inflammation is an extremely complex process which involves multiple signaling pathways. Hedgehog plays a role in this context but is a different and distinct pathway to that which has been identified in the context of the present invention. The fact that the present inventors have determined that activin is a crucial molecule in terms of the inflammatory cytokine cascade provides an alternative means of treating inflammatory conditions based on antagonizing activin. Applicant submits that Hedgehog is an intracellular signaling molecule. Activin is not an intracellular signaling molecule. The '216 publication is based on binding a molecule to the cell surface which sends a signal internally to down regulate Hedgehog signaling intracellularly or, presumably, to use a molecule that can be internalized by a cell in order to down regulate Hedgehog signaling. Activin is not an intracellular signaling molecule and one skilled in the art would not assume that any molecule which can down regulate intracellular signaling would necessarily have any role in terms of down regulating extracellular cytokine functionality as a means to down regulate the cytokine cascade which underpins the inflammatory response. The cytokine cascade is not an intracellular mechanism. In fact, a molecule that is shown to impact intracellular signaling is one that binds to or is internalized by a cell. Such an understanding would not lead one to conclude that a molecule that impacts intracellular signaling would act as an antagonist of an extracellular cytokine, especially one that plays no evident role in the signaling pathway. Additionally, cytokines, such as follistatin, are pleiotropic. The fact that follistatin may be shown to down regulate Hedgehog which therefore down regulates Hedgehog signaling and prevents production of BMP, does not inherently teach that which is claimed in the present application, i.e., that activin is in fact the crucial cytokine that regulates the inflammatory response and that antagonizing activin will achieve an effective anti-inflmnmatory response

However, it was known at the time the invention was made that sonic hedgehog (Shh) signaling can be triggered by activin A and inhibited by follistatin (see van Eyll et al, whole document and page 2085 last ¶). That is the activin is upstream of the hedgehog signaling pathway. Inhibiting activin with follistatin would lead to the inhibition of the Shh signaling pathway. Further, there is no alternative means of treating inflammatory conditions, both the prior art (`216) and the instant applicant use the same follistatin to treat the same inflammatory conditions.

Applicant submits that the '216 publication discloses that follistatin is an inhibitor of an intracellular signaling pathway, but provides absolutely no disclosure or teaching of the role of follistatin in the context of regulating the extracellular cytokine cascade via regulation of extracellular protein molecules, such as activin, or that follistatin actually has an impact on inflammation. In short, the '216 publication does not provide an enabling disclosure that would anticipate the claimed invention. A prior art reference must provide an enabling disclosure of the subject matter of the claim(s) against which it is cited. Elan Pharm., Inc., v. Mayo Found, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Mere naming or description of the subject matter is insufficient if it cannot be produced without undue experimentation. Id. Clearly the '216 publication is not enabling, at least as far as follistatin is concerned.

However, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which follistatin alleviates symptoms of inflammation does not appear to distinguish the prior art teaching the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. The reference teachings anticipate the claimed invention. The regulation of extracellular cytokine cascade would also all be intrinsic properties of follistatin and therefore are also all unpatentable over the prior art. The standard for what constitutes sufficient enablement of prior art reference for purpose of anticipation under 35 U.S.C. 102(b) differs from enablement standard under Section 112, in that the prior art reference need not demonstrate utility in order to serve as anticipating reference under Section 102. A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed in invention." In re Donohue, 766 F.2d 531,226 USPQ 619 (Fed. Cir. 1985). See MPEP 2121.01. "The reason is that section 112 "provides that the specification must enable one skilled in the art to 'use' the invention whereas [section] 102 makes no such requirement as to an anticipatory disclosure." Hafner, 410 F.2d at 1405; see 1 Donald S. Chisum, Chisum on Patents § 3.04[1][c] (2002); see also In re Cruciferous Sprout Litig., 301 F.3d 1343, 1349-52 (Fed.Cir.2002) (finding anticipation where applicant sought a patent based on a new use for a previously disclosed method)." Further, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 1, 2, 5-7, 10-12, 18, 19, 30 and 61-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over US20030162715.

The ` 715 publication teaches follistatin-3 protein binds to activin in a dose-dependent manner in the above-described assay (see ¶5, 22, 85), wherein it binds to activin A and B (see ¶560&563). The `715 publication teaches the use of follistatin-3 polypeptides to treat disease. For example, patients can be administered follistatin-3 polypeptides in an effort to replace absent or decreased levels of the follistatin-3 polypeptide, to supplement absent or decreased levels of a different polypeptide, to inhibit the activity of a polypeptide, to activate the activity of a polypeptide, to reduce the activity of a membrane bound receptor by competing with it for free ligand, or to bring about a desired response (see ¶338). The `715 publication further teaches that follistatin-3 polynucleotides or polypeptides cam also be useful in treating autoimmune disorders (see ¶391). Examples of autoimmune disorders that can be treated include, but are not limited to: rheumatoid arthritis or Autoimmune Pulmonary Inflammation (see ¶392). Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by follistatin-3 polynucleotides or polypeptides (see ¶393). The `715 publication teaches that follistatin-3 polynucleotides or polypeptides, can also be used to modulate inflammation. For example, follistatin-3 polynucleotides or polypeptides can inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.) (see ¶395). The `715 publication teaches a pharmacological composition of the invention use or sale for human administration (see ¶234, 235, 612).

The `715 publication differs form the claimed invention only in the recitation of follistatin in claims 1-2.

However, the `715 teaches we demonstrate that FLRG (follistatin-3) is a functional activin-binding protein which, like follistatin, binds both activin A and activin B. However, we demonstrate differential expression in tissues and regulation of follistatin and FLRG expression in cultured keratinocytes. Our results indicate differences in the in vivo regulation and functions of FLRG and follistatin proteins (see ¶549, ¶560). Further the family of inhibin-related proteins currently consists of at least four groups of members: inhibins, activins, and two splice variants of follistatin-1 (315 and 288 amino acids) (see ¶3). The ability of FLRG (follistatin-3) to associate with activin A was comparable to FS-315 and FS-288, as judged from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates. These results demonstrate that FLRG, like FS-315 and FS-288, can bind the unprocessed high molecular weight activin A precursor (see ¶563). Judging from the amounts of FLRG, FS-315, and FS-288 proteins in the immunoprecipitates, the ability of FLRG to co-immunoprecipitate activin B was at least as good as that of FS-315 and possibly even better than that of FS-288 (see ¶565).

Those of skill in the art would have had reason to use the follistatin of the `715 publication as a substitute for the treatment taught in the `715 publication because, like the follistatin-3 taught in `715 publication, follistatin are activin antagonist. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 1, 2, 5-7, 10-12, 18, 19, 30 and 62-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 8911862.

The WO `862 teaches the inhibin (activin antagonist) is useful in wound healing (see published claim 9), in the treatment of autoimmune diseases (see published claim 3), immunodeficiency diseases (see published claim 1), transplant rejection (see published claims 5, 8), and infection (inflammatory response to bacterial infection) (see published claim 2).

The `862 publication differs form the claimed invention only in the recitation of follistatin in claims 1-2.

However, the `862 publication teaches that the term "activin antagonist" as used throughout the specification and claims includes molecules having an activity or effect that is opposite to that of activin or that blocks or neutralizes the action of activin without necessarily combining with activin, as well as antibodies to activin or to its subunits, inhibin, and other inhibin-like molecules such as FSP, or follistatin (see page 3, lines 29-35).

Those of skill in the art would have had reason to use the follistatin of the '862 publication as a substitute for the treatment taught in the '862 publication because, like the inhibin taught in `862 publication, follistatin are activin antagonist. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. Claim 61 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 20020192216 as is evidenced by van Eyll et al (Jounal of Cell Science 117(10):2077-2086, 2003) or WO 8911862, each in view of WO/ 2003/006057.

The teachings of `862 and `216 publications and van Eyll et al have been discussed, supra.

The `216 differs from the claimed invention in the recitation of follistatin 288 or follistatin 315 in claim 61 and 71.

The `057 publication teaches that the activin antagonist is follistatin, or a fragment(s) or analogue thereof, and more typically the follistatin is a single chain protein comprising between 288 and 315 amino acids (see page 4, lines 16-19).

Those of skill in the art would have had reason to use the follistatin 288/315 of the '057 publication as a substitute for the treatment taught in the '216 publication because, like the compounds taught in `216 publication, follistatin 288/315 are activin antagonist. Substituting a known element for another, to yield the known result, is obvious. See KSR, 550 U.S. at 416, 421.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. The Russel et al. (Molecular and Cellular Endocrinology. 148(1-2): 129-136,1999) cited on the PTO-892, is to show that follostatin regulate the cytokine cascade.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 7, 2011

/Maher M. Haddad/
Primary Examiner,
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